tion for supplying the complex of boron fluoride and acetic acid, and to E. I du Pont de Nemours and Company for contributing the furan used in this investigation.

Summary

Thiophene and furan have been acylated with several aliphatic acid anhydrides in the presence of the complex of boron fluoride and acetic acid to give high yields of the corresponding 2-acyl derivatives.

Thiophene has been acylated with four acid chlorides in the presence of boron fluoride etherate in fair yields.

The direct acylation of thiophene with the complex of boron fluoride and acetic acid has given only a low yield of 2-thienyl methyl ketone.

PITTSBURGH, PA. RECEIVED OCTOBER 11, 1948

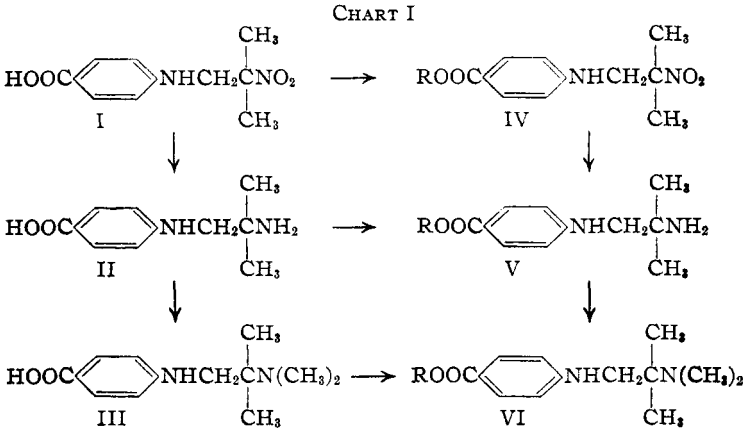
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DEPAUW UNIVERSITY]

Esters of Nitrogen-substituted *p*-Aminobenzoic Acid

BY J. M. FULMER AND HOWARD BURKETT

In 1942 it was suggested by Dr. H. G. Johnson[1] that from *p*-(2-nitro-2-methylpropylamino)-benzoic acid[2] (I) (see Chart I) alkyl *p*-(2-dialkylamino-2-methylpropylamino)-benzoates (VI, R = alkyl) be prepared and tested for local anesthetic activity. He synthesized *p*-(2-amino-2-methylpropylamino)-benzoic acid[2] (II) by the catalytic hydrogenation of I.

CHART I



The authors have made a number of esters (IV, V, VI) in which R is methyl, ethyl, *n*-propyl and γ-diethylaminopropyl, according to the equations shown. Methyl *p*-(2-amino-2-methylpropylamino)-benzoate (V, R = CH_3) was prepared in good yield both from the hydrogenation of the corresponding nitro-ester (IV, R = CH_3) and by the esterification of the acid (II). Using methyl sulfate, attempts to methylate the primary amine group in the acid (II) or the ester (V, R = CH_3) to give III or VI (R = CH_3), respectively, failed. However, no reactions were tried at elevated pressures. Use of the methylation procedure described by Clarke, *et al.*,[3] gave good yields in both cases.

All of the esters were prepared by direct esterification, except the γ-diethylaminopropyl esters, which were synthesized by the reaction of γ-diethylaminopropyl chloride on the sodium salt of the appropriate acid. The ethyl and *n*-propyl esters of VI were obtained only in poor yields by esterification. It was found in the case of the ethyl ester that better yields were obtained by the methylation of V (R = C_2H_5).

The pharmacological properties of these compounds are being studied by Graam, Ott and Schultz, who plan to publish their report in the *Journal of Pharmacology and Experimental Therapeutics*.

Acknowledgment.—The authors thank Dr. Jerome Martin for his suggestions and Commercial Solvents Corporation for the financial aid which made this investigation possible. The authors also thank Commercial Solvents Corporation for running all high-pressure hydrogenations and analyses.

Experimental

Procedure A. Ethyl *p*-(2-Nitro-2-methylpropylamino)-benzoate.—To a mixture of 25 g. of *p*-(2-nitro-2-methylpropylamino)-benzoic acid[2] and 150 ml. of ethanol was added 2 ml. of concd. sulfuric acid, with shaking. After refluxing for twelve hours, the reaction mixture was cooled and filtered. Two recrystallizations from ethanol yielded 15.7 g. (56%) of ester, m. p. 137–138°.

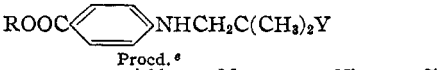
The methyl and *n*-propyl esters, as noted in Table I, were prepared in a similar manner. They were recrystallized from methanol and *n*-propanol, respectively.

Procedure B. γ-Diethylaminopropyl *p*-(2-Nitro-2-methylpropylamino)-benzoate.—To a suspension of 29.0 g. (0.12 mole) of finely powdered *p*-(2-nitro-2-methylpropylamino)-benzoic acid in 150 ml. of ethanol was added 72.5 ml. (0.12 mole) of a 1.660 *N* solution of sodium hydroxide in ethanol. After a few minutes, 19.8 g. (0.132 mole) of γ-diethylaminopropyl chloride, along with 50 ml. of ethanol, was added. After refluxing for four and one-half hours, the solution was filtered hot, collecting 7.0 g. of sodium chloride (theory was 7.0 g.). The filtrate was cooled overnight in the refrigerator. Filtration, followed by washing with ethanol and drying, gave 33.2 g. of the ester, m. p. 110–110.5°. Evaporation

(1) Private communication.
(2) H. G. Johnson, THIS JOURNAL, 68, 14 (1946).
(3) Clarke, Gillespie and Weisshaus, *ibid.*, 55, 4571 (1933).

TABLE I

SUBSTITUTED ALKYL *p*-(N-AMINO)-BENZOATES



R	Y	Procd.[e] yield, %	M. p., °C.	Nitrogen, % Calcd.	Found
CH_3	NO_2	A90	132.5–134	11.11	11.44
C_2H_5	NO_2	A56	137–138	10.50	10.15
$CH_3CH_2CH_2$	NO_2	A51	103–104	10.00	10.17
$(C_2H_5)_2N(CH_2)_3$	NO_2	B94	110–110.5	11.97	12.03
CH_3	NH_2	D82	79–80	12.61	12.60
CH_3	NH_2	C92[a]			
C_2H_5	NH_2	C74	65.5–66.5	11.87	12.09
$CH_3CH_2CH_2$	NH_2	C81	Oil	11.20	11.51
$(C_2H_5)_2N(CH_2)_2$	NH_2	B58	20–22	13.09	12.97
$(C_2H_5)_2N(CH_2)_3$	NH_2	D84	18–20		
H	$(CH_3)_2N$	E68	238 (dec.)[b]	11.87	11.73
CH_3	$(CH_3)_2N$	C60	90.5–91.5	11.20	10.74[c]
CH_3	$(CH_3)_2N$	E68	90.5–91.5		
C_2H_5	$(CH_3)_2N$	E66	70–71	10.60	10.57
C_2H_5	$(CH_3)_2N$	C12	72–73		
$CH_3CH_2CH_2$	$(CH_3)_2N$	C35[d]	65.5–66.5	10.08	10.33
$(C_2H_5)_2N(CH_2)_3$	$(CH_3)_2N$	B92	38–39	12.03	12.56

[a] This is the hydrochloride, m. p., 166–168° (dec.). [b] The hydrochloride melts at 256° (dec.). [c] Analysis after further drying: Calcd. for C, 67.20; H, 8.70. Found: C, 67.40; H, 8.39. [d] Yields for other runs of this compound were much lower. [e] Letter preceding percentage yield represents procedure followed.

to one-fourth volume, adding water and cooling gave an additional 6.4 g. (94% yield).

The other γ-diethylaminopropyl esters (V and VI, R = $(C_2H_5)_2N(CH_2)_3$) were prepared in a similar way with the following exceptions. After refluxing, the solvent was removed under reduced pressure, water was added and the product was extracted with ether. After washing the ether solution with dilute sodium carbonate solution, the ether was evaporated. Solid esters were recrystallized from petroleum ether.

Procedure C. Methyl *p*-(2-Amino-2-methylpropylamino)-benzoate.—A suspension of 9 g. of finely divided *p*-(2-amino-2-methylpropylamino)-benzoic acid[2] in 100 ml. of methanol was saturated with dry hydrogen chloride, finally with cooling in ice. After standing at room temperature overnight, the reaction mixture was refluxed for twenty minutes. After cooling in the refrigerator, the mixture was filtered and washed with methanol, yielding 11.7 g. of the hydrochloride of the ester, V (R = CH_3).

A portion of the hydrochloride was dissolved in water. Upon adding sodium hydroxide, the ester, m. p. 79–80.5°, precipitated.

Other esters required refluxing for a longer time (up to twenty-four hours) in order to get satisfactory yields. In most cases the product was isolated as described in the last paragraph under Procedure B.

Procedure D. Methyl *p*-(2-Amino-2-methylpropylamino)-benzoate.—A solution of 130 g. of methyl *p*-(2-nitro-2-methylpropylamino)-benzoate in 1000 ml. of methanol, to which was added 10 g. of Raney nickel, was hydrogenated at 100° and 1000 p.s.i. After filtering off the catalyst, the methanol was distilled and the remaining liquid distilled under reduced pressure. There was obtained 94.5 g. of the ester, b. p. 160–161° at 1 mm., which solidified upon standing, m. p. 79–81°.

γ-Diethylaminopropyl *p*-(2-nitro-2-methylpropylamino)-benzoate was hydrogenated in benzene. The amine was purified by washing with aqueous sodium hydroxide, drying over anhyd. sodium carbonate and removing the solvent under reduced pressure.

Procedure E. *p*-(2-Dimethylamino-2-methylpropylamino)-benzoic Acid.—To 41.6 g. (0.2 mole) of *p*-(2-amino-2-methylpropylamino)-benzoic acid was added 50 ml. of formalin and 52 ml. of 98% formic acid. In about fifteen minutes the flask was placed in an oil-bath heated to 140° and the mixture was allowed to reflux for four hours. After adding 24 ml. of concd. hydrochloric acid to the hot reaction mixture, it was evaporated to dryness under reduced pressure with warming on the steam-bath. After adding 50 ml. of warm water and cooling in the refrigerator, the mixture was filtered and the solid washed with water, yielding 37.1 g. of the hydrochloride of the acid, m. p. 256° (dec.).

A sample of the hydrochloride was dissolved in boiling water and sufficient 20% aqueous sodium hydroxide was added to make the solution faintly basic. Filtering and washing with hot water gave the free acid, m. p. 238° (dec.).

Esters prepared in this manner were purified as in Procedure C.

Summary

A number of esters of *p*-(2-nitro-2-methylpropylamino)-, *p*-(2-amino-2-methylpropylamino)- and *p*-(2-dimethylamino-2-methylpropylamino)-benzoic acid have been prepared.

GREENCASTLE, INDIANA RECEIVED NOVEMBER 15, 1948

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Ring Substituted Benzoylacrylic Acids as Antibacterial Agents

BY FRED. K. KIRCHNER, JOHN HAYS BAILEY AND CHESTER J. CAVALLITO

In an investigation of model antimicrobial compounds containing unsaturated lactone or carbonyl structures, one of the types which appeared to be of interest because of its solubility and activity against both gram positive and gram negative bacteria was benzoylacrylic acid. Worrall[1] has reported antibacterial activity of methyl and propyl esters of the acid and Rinderknecht, *et al.*,[2] have observed activity of the acid as well as the *p*-chloro-, 2,4-dichloro- and *p*-acetamido derivatives.[2,3]

Observations have been made relative to some non-ionic antibiotics that the degree of activity against gram positive bacteria was associated with the lipophilic properties of the compound.[4,5] It was of interest to determine whether this relationship could be shown with the anionic benzoylacrylic acids.

Para alkyl-substituted β-benzoylacrylic acids

(1) Worrall, "Med. World" (London), 1946, 2 pp., *C. A.*, **41**, 6598 (1947).

(2) Rinderknecht, Ward, Bergel and Morrison, *Biochem. J.*, **41**, 463 (1947).

(3) British Patent 588,108; *C. A.*, **42**, 329 (1948).

(4) Small, Bailey and Cavallito, THIS JOURNAL, **69**, 1710 (1947).

(5) Cavallito and Bailey, *J. Bact.*, in press.